Remarks/Arguments

No new matter is believed to be added with any amendments made herein.

Regarding amendments to the claims

New claims 105-114 are added with this amendment. Support for these claims may be found throughout the present application, including for instance the Examples and description thereof, and for instance page 22 lines 9-29, page 23 lines 10-13 of the application as filed.

Claim 88 is amended to refer to the pharmaceutical composition of claim 54, and claim 89 is amended to remove redundant information in the claim, in keeping with US practice.

Regarding amendments to the specification

Page and line references are to the application as filed.

A paragraph describing related applications is inserted at the beginning of the application, in keeping with US practice.

Amendments to pages 1, 13, 38 (lines 7-10) and 42 refer to publication numbers of equivalent versions of said documents.

Amendments to pages 38-39, 42-45, 47-48, 51, 53-56 are to correct typographical errors and references to Figures and data therein, and are supported throughout the application and in particular by the Figures. Page 53 lines 23-30 is amended to report findings in Figures 9 a-c, and is supported by Figures 9a-c. Page 55 lines 22-26 now correctly refers to Examples 30-35; support for this amendment may be found for instance at Examples 30-35 and 54-58, and their related Figures.

Response to 112 enablement rejection of the term "active ingredient"

At pages 2-4 of the present Action, the Examiner rejects all of the pending claims (54-63 and 65-103) under 35 USC 112 first paragraph as lacking enablement, stating that the rejection is as set forth on pages 2-4 of the Office Action mailed April 3, 2008. The Examiner then kindly points out those aspects of the previous rejection that have been overcome, and states that the specification is enabling for an active ingredient that is a peptide or protein, but not for any non-protein/non-peptide active ingredient. The rejection explains that because Santus (US 6,333,044) column 2 lines 40-59 teaches that many therapeutic agents may not be administered transnasally, and that the ability of drug molecules to be absorbed by the nasal mucosa is "utterly unpredictable" (as is toxicity to mucous membranes), only proteins and peptides are enabled by the present application in view of their successful transnasal administration in the Examples.

In response, Applicant respectfully submits that the term "active ingredient" in the present claims is enabled by the application as filed under 35 USC 112, first paragraph. As discussed below, Santus column 2 lines 40-59 discloses that the ability of any given drug to be absorbed across the nasal mucosa is "utterly unpredictable", and that the few drugs that may be so absorbed need specially

tailored formulations for effective absorption across the nasal mucosa. In contrast, penetrants of the present invention do not administer active ingredients by simple absorption. The present invention is believed to target pores of the nasal mucosa for active ingredient administration, thus avoiding problems with mucous membrane irritation that plague the prior art. The Examples of the present invention alone illustrate the transnasal administration of over 11 substances with one method, in contrast to Santus' disclosure of the transnasal administration of one drug (and report of 8 others) by different methods. Furthermore, the present application (including the Examples) discloses the transnasal administration of non-protein/non-peptide substances. At least for these reasons, discussed in further detail below, Applicant respectfully requests that the Examiner withdraw this rejection accordingly.

i. The state of the art, Santus[1], and the present invention

The present application discusses state of the art attempts to administer drugs across the nasal mucosa by formulating a given drug with a "permeation enhancer" or "absorption enhancer" (typically a surfactant). Such enhancers are believed to work by loosening tight cell-cell contacts in the nasal mucosa, allowing water and drug to pass through the mucosa. The enhancers also typically irritate the nasal mucosa, as such loosening is inherently damaging to the mucosal surface, so that increasing amounts of enhancers typically provide for increased transnasal drug delivery but also increased toxicity. See for instance bottom page 1 to top page of 3 of the application as filed (particularly page 2 lines 22-27 and page 2 line 34 to page 3 line 2), disclosing known difficulties with conventional absorption of drugs (particularly high molecular weight proteins) from the nasal mucosa; page 6 line 26 to page 7 line 26, disclosing damage caused by absorption enhancers to nasal mucosa; and page 9 lines 4-16, disclosing dose-dependent toxicity/irritation to the nasal mucosa.

Santus column 2 lines 40-59 reports on state-of-the-art problems similar to those discussed in the present application. Santus column 2 lines 40-59 expressly states that many therapeutic agents cannot be nasally administered because each agent's absorption (line 53) is "utterly unpredictable", and that only a very few molecules, each presented in its own "special formulation", may be transnasally administered. Santus then discloses a special formulation for the transnasal administration of 5-benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid (Ketorolac®) with an "absorption promoter" or other substance that will aid in the absorption of the drug across the nasal mucosa. See e.g. Santus column 2 lines 12-31 (including Santus' reference to "absorption promoter" at column 2 line 29 and column 4 lines 6-14), column 8 lines 60-66 (emphasizing Santus' administration method is via simple absorption), and column 10 lines 61-67 (indicating best absorption of Ketorolac® with a formulation including EDTA and glycocholate).

Overall, Santus and the state of the art teach that if one formulates a specific drug with a specific absorption/permeation enhancer (e.g. surfactant) and then applies the formulation directly to the nasal mucosa, the drug may be able to be administered transnasally, although such administration will likely also cause dose-dependent mechanical or chemical damage (and therefore irritation) to the nasal mucosa. As this approach requires drugs to directly interact with the damaged surface of the nasal mucosa, state of the art formulations may vary widely in view of physico-chemical characteristics of drug, enhancer(s), and the nasal mucosa.

[1] Applicant does not intend to admit or indicate in any way that the cited Santus patent is part of the state of the art relevant to the present invention for the purposes indicated by the Examiner.

The present invention does not transnasally administer active ingredient via simple absorption/permeation, in contrast to the state of the art and Santus (see also pages 14-16 of the present application, contrasting penetration by the present penetrants with state of the art permeation/permeants)[2]. Pending claim 54 is directed, in part, to a penetrant capable of administering drugs across the nasal mucosa in a manner believed to exploit already-existing passageways in the mucosa – mucosal pores. While state of the art surfactants may be used to prepare penetrants of the present claims, the present claim 54 surfactants are incorporated into a layer surrounding a droplet to form a penetrant. Such penetrants do not simply smear drug and surfactant across the nasal mucosa to create openings in the mucosa, but rather retain their integrity as minute, deformable droplets that may be driven/forced into already-existing openings (mucosal pores) to administer the drug. See for instance page 15 line 26 to page 16 line 7 and bottom page 16 to top page 17 of the present application, noting that membrane metastability of penetrant droplets of the present claims allows for "unusually high local bilayer curvature", so the penetrant droplets may maintain their integrity and enter mucosal pores without disintegrating and spreading potentially irritating drug and surfactant over the nasal mucosa to achieve delivery. See in particular page 17 lines 1-14, disclosing that penetrant droplets transported across pores in the nasal mucosa work differently than do state of the art absorption enhancers/compositions, as the penetrant droplets do not appear to damage the barrier or to work in a penetrant-dose-dependent manner. Conversely, in some cases, increasing the concentration of surfactant molecules in a penetrant actually decreases the efficiency of transnasal administration, when the solubilization point of the surfactant making up the penetrant droplet has been reached (page 9 lines 1-12 of the present application).

Essentially, the present invention elegantly by-passes problems of the state of the art by presumably administering active ingredients through existing mucosal pores, avoiding problems with using enhancers to facilitate drug absorption by forcing openings therein and damaging the nasal mucosa. Applicant further notes that damage to the nasal mucosa may be caused by the drug itself – for instance, Cholera toxin (CT) is typically considered difficult to administer transnasally in view of toxicity from its ADP-ribosylation activity. However, transnasal CT administration appears well-tolerated in the present application, presumably in part because the present penetrants limit CT's exposure to the nasal mucosal surface. See for instance page 2 lines 5-11 (discussing CT toxicity); page 17 line 31 to page 18 line 2 (discussing the surprising lack of toxicity from administering large immunogens with the present method) and bottom page 32 to top page 33 (disclosing successful immunogen administration, with or without cytokines, that cause no irritating side effects).

At least in view of the foregoing comments, Applicant respectfully submits that one skilled in the art would view Santus's disclosure at column 2 lines 40-59 as relating to the unpredictability of absorption (permeation) of drugs through the nasal mucosal surface. As discussed above, the penetrants of the present invention administer drugs by penetrating mucosal pores, not by absorption (permeation). Applicant respectfully requests that the Examiner disregard Santus' disclosure in the context of the present invention therefore.

[2] Not to be bound by theory, as indicated here and as otherwise discussed through this Amendment. Differences between penetrants of the present invention and traditional permeants/permeation techniques are described throughout the application.

ii. The present Examples disclose the transnasal administration of non-peptide, non-protein active ingredients

With regard to the Examiner's concern that no active ingredients other than proteins/peptides are transnasally administered in the present Examples, Applicant respectfully notes that several Examples of the present application demonstrate the transnasal administration of non-protein/non-peptide substances.

At a minimum, the present Examples show the transnasal administration of monophosphoryl lipid A ("LA")[3]. LA is known as a glycolipid and as a lipopolysaccharide. The administration of LA may be construed as showing the present invention effectively transnasally administers a lipid (which includes sugar moieties) and a carbohydrate (which includes lipid moieties), so that the molecule provides its expected activity. See for instance Examples 30-35, 54-58 of the present application (pages 52-53; 55), disclosing the transnasal administration of LA. See also the bottom of page 52 and Figures 8a-8c, disclosing that LA "worked as expected", and page 55 and Figure 12, disclosing that LA combined with tetanus toxoid (TT) and IL-12 provided different results than LA and tetanus toxoid alone.

See also for instance Examples 22-29 and Figures 7a, et al., disclosing the administration of "impure" tetanus toxoid via the present invention. Penetrants containing the impure toxoid were prepared with a filtrate from *in vitro* Clostridium tetani culture (page 51 lines 8-9). The filtrate contained tetanus toxin expressed into the medium by the C. tetani cells, as well as substances needed for cell growth (e.g. glucose, ammonium salts, trace elements and amino acids) and cell waste or other materials excreted or secreted into the culture medium by the cells. Although the effect of these substances may not have been directly measured, given the present invention's demonstrated capacity for administering a wide variety of drugs with a wide variety of biological activities (see for instance Examples 54-58 and Figure 12, disclosing co- administration of large antigen molecules, and small cytokines and monophosphoryl Lipid A), one skilled in the art would assume these substances, like the accompanying TT, were transnasally administered.

At least for the foregoing reasons, Applicant respectfully submits that the present Examples disclose the transnasal administration of non-protein / non-peptide substances, and requests that the Examiner withdraw the present rejection.

Applicant also points out for instance Examples 167-72 of US Patent No. 6,165,500 (equivalent to PCT/EP91/01596, incorporated by reference at page 13 of the present invention to describe penetrant formulations of the present invention). These Examples disclose effective transdermal administration of prostaglandin E1 (a lipid). While Applicant recognizes such administration was transdermal and not transnasal, Applicant notes that such formulation clearly associates penetrants of the present invention with a lipid such as prostaglandin E1. One skilled in the art, in view of the variety of substances and their various biological activities administered transnasally in the present Examples, would likely understand that a penetrant of the present claims could transnasally administer prostaglandin E1 as well.

iii. The present invention is enabling for non-protein/non-peptide active ingredients.

[3] LA is disclosed as a preferred active ingredient at page 23 line 12 of the application as filed, and as a preferred adjuvant at page 35 line 22 of the application as filed.

Applicant respectfully submits that the term "active ingredient" of the present claims is enabled by the application under 35 USC 112. With regard to the Examiner's concerns regarding Santus column 2 lines 40-59 and the unpredictability of transnasal administration, Applicant notes the present invention works via penetration, not permeation (absorption), and thus avoids difficulties in delivery and toxicity from simple absorption techniques. With regard to the Examiner's concern that only peptides/proteins are enabled by the present Examples, Applicant notes that the present Examples include instances of the transnasal administration of non-protein non-peptide substances.

Applicant further submits it would be unfair to require Applicant to restrict the present claims to just one structural group of active ingredients such as proteins/peptides. Consider again, for instance, Santus column 2 lines 40-59 (cited in part):

> At present, the molecules which have proved suitable for this route of administration are still very few and consist essentially of only small peptide or hormone molecules (such as calcitonin, cerulean, .beta.-endorphin, glucagon, horseradish peroxidase, B-interferon, oxytocin and insulin) in special formulations. The ability of drug molecules to be absorbed by the nasal mucous membranes is utterly unpredictable, as is the ability of intranasal formulations to avoid irritation of the mucous nasal membranes.

Now consider the large number of substances shown to have been successfully intranasally administered in the present Examples, some alone, some in combination with others (listed in order of appearance in Examples):

1. Human recombinant insulin
2. ^{125}I-labelled insulin
3. IFN-gamma
4. Tetanus toxoid – impure preparation
5. Tetanus toxoid – pure preparation
6. GM-CSF
7. IL-4
8. IL-12
9. Monophosphoryl lipid A (LA)
10. Cholera toxin
11. Heat labile toxin

Santus lists a total of 9 substances (including Ketorolac®) as intranasally administrable; all needing their own "special formulations" for said administration. The present Examples exemplify the successful administration of 11 substances, all by the present method. Except for insulin, each substance administered in the present Examples is different from substances listed by Santus. One skilled in the art, reading Santus, would not likely expect that the 'very few" molecules listed by Santus could be literally doubled by one new method of transnasal administration.

Applicant expressly included the above substances in the Examples in part to illustrate that even difficult-to-administer high-molecular weight proteins and/or antigens[4] may be effectively administered via the present method. See also for instance page 22 lines 18-20, and similar disclosures throughout the present application, mentioning that a preferred embodiment of the present invention is to include an active ingredient that does not cross the nasal mucosa in a practically meaningful quantity without inacceptable side effects. Furthermore, as noted for instance at pages 48-49 of the present application and at Figure 4, the present invention allows for the administration of different size molecules while preserving their different activities (ex. antigens and cytokines). It would be unfair to limit Applicant's invention to only non-protein/non-peptide molecules, when penetrants of the present invention may associate with and transnasally administer a wide variety of active ingredients, as described throughout the present application. Furthermore, as high molecular weight proteins are generally considered among the most difficult substances to administer transnasally, one skilled in the art would be able to discern that other molecules, including potentially large or small molecules such as carbohydrates and lipids, could also be administered via the penetrants and method of the present invention.

Accordingly, Applicant submits that the application as filed is sufficiently complete to enable one of ordinary skill in the art to make and use the claimed invention without undue experimentation, and requests that the Examiner withdraw this rejection.

Respose to 112 enablement rejection of lipids/surfactants

At pages 2-4 of the present Action, the Examiner rejects all of the pending claims (54-63 and 65-103) under 35 USC 112 first paragraph as lacking enablement, stating that the rejection is as set forth on pages 2-4 of the Office Action mailed April 3, 2008. The Examiner then kindly points out those aspects of the previous rejection that have been overcome, and states that the specification is enabling only for a penetrant comprising soybean phosphatidylcholine (SPC; lipid) and either Tween 80 or sodium cholate (surfactants). The Examiner then states that one skilled in the art would not know how to make or use the present invention with other lipids or surfactants without undue experimentation, in view of Santus' teachings (discussed above), and because the application has not demonstrated well-tolerated transnasal administration using any other lipid or surfactant combination.

In response, Applicant respectfully submits that one skilled in the art can make and use the present invention with other lipids and surfactants without undue experimentation. First, Applicant respectfully directs the Examiner to the above discussions of Santus and the present invention, and submits that one skilled in the art would recognize that Santus' teaches the unpredictability of transnasal administration from known permeation (absorption) administration, where surfactant is applied to the nasal mucosa to loosen/damage cell-to-cell contacts and typically provide for dose-dependent drug delivery and mucosal irritation. In contrast, the present invention by-passes simple absorption techniques such as those outlined by Santus, penetrating already-existing passages (pores) in the nasal mucosa rather than damaging the mucosa. The penetrants may contain surfactants that would irritate the nasal mucosa in such permeation/absorption methods, but as the present penetrants are deformable, they do not spread such irritants all over the mucosa in the same manner as state of the art absorption techniques.

[4] See for instance the present application as filed page 1 lines 17-19 and 26 – page 2 line 15, page 2 line 34 – page 3 line 15, et al.

See for instance page 16 bottom to page 17 top of the application as filed, generally disclosing no irritation in the nose from several successfully tested formulations of the present invention. See also page 43 lines 9-10 and page 44 lines 6-7l disclosing no local adverse side effects after the nasal administration of insulin, and page 2 lines 5-11, page 17 line 31 to page 18 line 2, and bottom page 32 to top of page 33, discussing CT toxicity and the surprising lack of toxicity from administering large immunogens, with or without cytokines, by the present invention.

In addition to penetrants prepared with SPC (lipid) and either Tween 80 or sodium cholate (surfactants), the present Examples disclose penetrants made with the lipid soybean phosphatidylglycerol in conjunction with SPC (e.g. Example 1), and with the surfactant 50% ionized cholic acid (e.g. Examples 6-9, 10-11). One skilled in the art would know from the present application that if penetrants made with known mucosal irritants[5] such as cholic acid or sodium cholate were not irritating to the nasal mucosa, the present penetrants and method did not apply such substances to the nasal mucosa in a manner typical in the state of the art.

At least in view of the foregoing discussion, Applicant respectfully submits that one skilled in the art would not be concerned about nasal mucosa toxicity described by Santus from the present invention. The application and particularly the Examples would confirm to one skilled in the art that surfactants in penetrants of the present invention do not exhibit the same toxicity as surfactants applied according to state of the art methods. As undue experimentation to identify non-toxic lipids and surfactants would not be necessary for one skilled in the art, Applicant respectfully requests that this rejection be withdrawn therefore.

As a further note, Applicant respectfully points out page 13 lines 21-26 of the application as filed, incorporating by reference other exemplary penetrant formulations of the present invention (for instance PCT/EP91/01596 (equivalent to US 6,165,500) and PCT/EP96/04526 (equivalent to US 2002/0048596)). Penetrant formulations in these documents include lipids such as a combination of SPC and phosphatidylglycerol (US 6,165,500; Examples 32-39, col. 55), similar to present Example 1; dipalmitoyltartric acid ester (Examples 120-128), phosphatidylethanolamine N fluorescein (Examples 137-139), dipalmitoylphosphatidylcholine (Examples 146-150); and surfactants such as oleic acid (US 6,165,500; Examples 1-13); sodium deoxycholate (Exs. 92-98); sodium lauryl sulfate (Exs. 120-128); octyl-glucopyranoside (Exs. 129-136); Brij 35 (PEG(23) lauryl ether, Examples 146-148); bile acid (sodium salt; Exs. 151-157)); didecanoylphosphatidylcholine (US 2002/0048596; Exs. 5-6); diclofenac (Exs. 8-17) and ibuprofen (Exs. 18-25). Such disclosures provide further guidance to those skilled in the art as to how to make and use the present invention without undue experimentation.

Summary of response to rejections under 35 USC 112

At least in view of the foregoing discussion, Applicant submits that one skilled in the art would understand that Santus' disclosure of unpredictable absorption/permeation of drugs across the nasal mucosa is not applicable to the present invention, which presumably by-passes problems with traditional absorption methods by penetrating nasal mucosa pores. Also, one skilled in the art would note the transnasal administration of a large number of different molecules in the present Examples, in contrast to the state of the art, including non-protein/non-peptide molecules and including large and

[5] See for instance the first paragraph under "Discussion" in Drejer et al., Diabetic Medicine 9:335-340 (1992), disclosing that bile salts and their derivatives provided "considerable" local irritation when used as enhancers.

small protein/peptide molecules with intact and varied biological activity. Further, one skilled in the art would likely understand that the present method may be used to transnasally administer virtually any active ingredient, for instance as indicated at pages 20-26 of the application as filed, therefore. Finally, one skilled in the art could make and use the present invention without undue experimentation, as one skilled in the art would expect that lipids and surfactants of the present invention be well-tolerated.

At least for the foregoing reasons, Applicant submits that one skilled in the art would be able to make and use the present invention without undue experimentation, based on the application as filed, and respectfully requests that the Examiner withdraw the present rejection.

Response to rejection under 35 USC §112, first paragraph – written description

At pages 5-6 of the present Action, the Examiner rejects pending claims 54-63 and 65-103 as lacking an adequate written description under 35 USC 112 first paragraph, stating that nasal administration of substances is notoriously unpredictable both with regard to administration of substances and toxicity from such administration, and that only those penetrant compounds described in the Examples, comprising SPC and either sodium cholate or Tween 80, are adequately described under the written description requirement. The Examiner therefore seeks to limit the present claims to only an active ingredient that is a peptide or protein, a lipid that is SPC and a surfactant that is sodicum cholate or Tween 80.

In response, Applicant respectfully directs the Examiner to the above discussion regarding Santus, the present Examples, and the enabling disclosure of the present invention. Nasal administration of substances may be unpredictable for conventional absorption methods, where drug delivery is tailored to each drug and typically provides dose-dependent toxicity. However, as discussed above, the present method by-passes unpredictability problems in the state of the art, presumably by delivering active ingredients through existing mucosal pores, avoiding the need for applying surfactants/enhancers to disrupt and irritate the nasal mucosa.

One skilled in the art would understand, upon reviewing the application, that the present application shows possession of the claimed invention when filed. Penetrants of the present invention may deliver a wide variety of active ingredients, and may use a wide variety of lipids and surfactants, as they maintain their integrity upon transnasal administration, exploiting exisiting mucosal pores and thereby by-passing mechanisms of absorption and their resultant irritation/toxicity. The present Examples set forth ample description of the present invention, and the application further indicates other active ingredients, lipids and surfactants that may be used in the present invention for transnasal delivery.

At least in view of the foregoing comments, Applicant respectfully submits that the present application as filed clearly shows possession of the present invention, and respectfully requests that the Examiner withdraw the present rejection.

* * * *

Applicant respectfully submits that the present Amendment places the present application in condition for allowance, and respectfully requests that the Examiner allow the application proceed to grant therefore.

Respectfully submitted,

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